REMARKS

Applicants request entry of this amendment and reconsideration of the rejection of the claims.

Applicants have cancelled claim 24 without prejudice. Applicants reserve the right to pursue the subject matter of claim 24 in a continuation application. Applicants have amended claims 15 and 25. Applicants submit the amendment to the claims are supported throughout the specification and do not raise any issues of new matters. Claim 15 has been written in independent form and the dependency of claim 25 has been corrected so that it now depends from claim 14, rather than cancelled claim 24.

Interview

Applicants would like to thank Examiner Zeman and his supervisor Donna Wortman for the interview conducted on July 10, 2002.

35 U.S.C. § 103

The Examiner has rejected claims 34-37 and 39-43 under 35 U.S.C. § 103 as being unpatentable over Foster in view of Ashkenazi and Rickles. Applicants respectfully traverse the rejection.

Applicants submit that the Examiner has not established a *prima facie* case of obviousness, because the Examiner has failed to cite references that disclose all of the elements of the claimed invention and there would be no motivation to combine these references, because they do not in combination provide Applicants' claimed invention.

Claim 34 is directed to a DNA construct comprising a first DNA segment comprising a nucleic acid sequence that encodes a mammalian t-PA prosequence operably linked to a nucleic acid sequence that encodes a presequence other than a mammalian t-PA presequence and a second DNA segment operably linked to the first DNA segment, wherein the second DNA segment encodes a heterologous glycoprotein.

Applicants submit that the Foster reference does not teach or suggest a nucleic acid sequence that encodes a mammalian t-PA prosequence operably linked to a nucleic acid sequence that encodes a presequence other than a mammalian t-PA presequence. The Foster

reference discloses the use of the secretory sequence from t-PA having 35 amino acids and further that the secretory sequence should be modified by amino acid substitutions to avoid cleavage resulting in additional N-terminal amino acids. (See col. 7, lines 39-45, col. 8, lines 28-44). Foster does not teach or suggest that the prosequence of the mammalian t-PA can be operatively linked with a presequence other than the mammalian t-PA sequence.

The deficiencies of Foster are not remedied by reference to Ashkenazi or Rickles. As discussed previously, Ashkenazi discusses TNFR-IgG, but does not teach or suggest that any other signal sequence or prosequence should be linked with TNFR-IgG. Rickles disclose isolation and purification of a cDNA encoding a murine tissue plasminogen activator as a probe to analyze t-PA expression. The Rickles reference does not disclose or suggest the linking of a t-PA prosequence with a presequence other than a mammalian t-PA presequence.

Thus, the combination of these references does not disclose all of the limitations of claims 34-37 and 39-43. Moreover, one of skill in the art would not be motivated to combine these references, because Ashkenazi and/or Rickles do not even discuss or suggest combining any other signal sequence with a TNFR-IgG or other glycoprotein and, therefore, one of skill in the art would not be motivated to combine these references with Foster.

The Examiner has indicated that the motivation to combine the references is based on the teaching concerning t-PAs from non-human sources in Foster and Rickles. The disclosure of a murine tPA signal sequence does not make obvious Applicants' claimed invention because none of the references disclose the linking of a mammalian t-PA prosequence with a presequence other than a mammalian t-PA presequence. Thus, Applicants respectfully request withdrawal of the rejection of claims.

The Examiner has also rejected claims 14 and 16-46 under 35 U.S.C. § 103 as being unpatentable over Foster in view of Ashkenazi and Berman and Lasky. Applicants respectfully traverse the rejection.

Applicants submit that the Examiner has not established a *prima facie* case of obviousness because the cited references do not disclose all of the elements of the claimed invention, and secondly because there would be no motivation to combine the references as cited by the Examiner.

Claim 14 is directed to a DNA construct comprising a first DNA segment encoding a precursor polypeptide comprising a prosequence of a mammalian t-PA and a second DNA

segment operably linked to the first DNA segment, the second DNA segment encoding a heterologous glycosylation site deletion variant glycoprotein.

As discussed previously, none of the cited references teach or suggest glycosylation site deletion variants. These references also do not indicate that glycosylation site variant glycoproteins have secretion problems or that a prosequence from a mammalian t-PA would solve the problem. The Foster reference is directed to increasing the secretion of glycosylated thrombopoietin. There is no teaching or suggesting in Foster that the use of a t-PA prosequence could enhance secretion of glycosylation site variant glycoproteins, especially glycosylation site deletion variant proteins. The reference does not even mention that thrombopoietin is a glycoprotein or discuss glycosylation at all. The Examiner admits that the reference does not disclose glycosylation deletion site variants.

The deficiencies of Foster are not remedied by reference to Ashkenazi or Berman and Lasky reference. Ashkenazi, as discussed previously, is directed to description of TNFR-IgG and does not describe glycosylation site deletion variants. The Berman and Lasky reference does not remedy the deficiency of these references because the reference does not teach or suggest that glycosylation site deletion variants can and should be made for expression in eukaryotic cells or that such variants would have alterations in secretion from eukaryotic cells. The Berman and Lasky reference compares expression of fully glycosylated proteins in mammalian cells to production of glycoproteins in E. Coli. This paper is directed to the advantages of producing fully glycosylated proteins compared to producing proteins in E. Coli. As disuussed in the reference, those advantages are that glycosylation is important for proper folding, cellular transport, prolongation of half-life and antigenicity. The authors therefore conclude it is more advantageous to produce glycosylated proteins in mammalian cells than aglycosylated proteins in bacteria. Thus, Berman and Lasky do not teach or suggest that glycosylation deletion variants can or should be made or expressed in eukaryotic cells and in fact, teaches that expression of proteins lacking glycosylation is disadvantageous. Thus, the Examiner has not cited references that disclose all of the elements of the claimed invention.

Furthermore, one of skill in the art would not be motivated to combine these references to obtain the claimed invention, because none of the references are directed to glycosylation site deletion variants and/or secretion of glycosylation site deletion variants.

Thus, Applicants respectfully request withdrawal of the rejection.

NEW CLAIM OBJECTION

The Examiner has objected to claim 24 of being of improper dependent form. Applicants have canceled this claim rendering the rejection moot. Therefore, Applicants respectfully request withdrawal of the rejection.

IDS STATEMENT PREVIOUSLY SUBMITTED

Applicants note that an IDS Statement was submitted on January 7, 2000. (Copy enclosed). Applicants note that they have not received the initialed 1449 form. Applicants request that the Examiner consider the references and initial the 1449 form and return a copy to Applicants.

SUMMARY

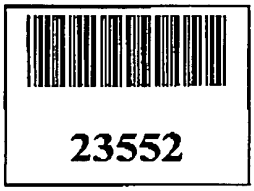
Applicants submit that all of the claims are in condition for allowance. Applicants respectfully request notification to that effect. Applicants note that they have written claim 15 in independent form.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: July 25, 2002

Katherine M. Kowalchyk
Reg. No. 36,848
KMK:sab



MARKED-UP VERSION SHOWING CHANGES

15. (AMENDED) [The] A DNA construct [of claim 14 further] comprising [one or more additional DNA segments operably linked to the first and second DNA segments] a first DNA segment encoding a precursor polypeptide comprising a prosequence of a mammalian t-PA and a second DNA segment operably linked to the first DNA segment, the second DNA segment encoding a heterologous glycosylation site deletion variant glycoprotein and one or more additional DNA segments operably linked to the first and second DNA segments.

25. (AMENDED) The DNA construct of claim [24] 14, wherein the heterologous glycosylation site variant is an immunoadhesin.